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(54) Title: COMPOSITIONS COMPRISING L–ARGININE, GINSENG AND GINGKO BILOBA FOR ENHANCING BLOOD CIRCULATION

(57) Abstract

The invention provides methods and compositions for maintaining a state of wellness in a human by providing a dietary supplement comprising L–arginine, in combination with ginseng and gingko biloba and/or additional nutritional supplements. The invention provides a unique blend of components that, in combination, synergistically bestow cardiac and sexual wellness upon a human when taken regularly as a dietary supplement alone, or in combination with a pharmaceutical composition (e.g. Viagra), which facilitates smooth muscle relaxation and vascular dilatation.

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COMPOSITIONS COMPRISING L–ARGININE, GINSENG AND GINGKO BILOBA FOR ENHANCING BLOOD CIRCULATION

INTRODUCTION

Technical Field

This invention relates to the maintenance of a state of wellness in which cardiac and sexual health is enhanced.

Background

Quality of life is increasingly valued in today's society. Proper nutrition and exercise, and healthy sexual function contribute to maintain an overall state of wellbeing, which can serve to manage stress, maintain a properly functioning immune system, protect against disease, maintain a positive mental outlook, and generally to enable one to feel good and enjoy life. It has been found that the combination of L-arginine, ginseng, and ginkgo biloba when administered to a human in combination enhances the blood circulation and improves the sexual, mental, and cardiac health of an individual.

SUMMARY OF THE INVENTION

The invention provides methods and compositions for maintaining a state of wellness in a human by providing a dietary supplement comprising L-arginine, in combination with ginseng and ginkgo biloba and/or additional nutritional supplements. The invention provides a unique blend of components that, in combination, synergistically bestow cardiac and sexual wellness upon a human when taken regularly as a dietary supplement alone, or in combination with a pharmaceutical composition which facilitates smooth muscle relaxation and vascular dilatation. The invention also provides methods and compositions for maintaining wellness by administering an amount of the L-arginine composition to reduce the incidence of headache, gastric upset and/or increase the ease of breathing upon exertion.

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DESCRIPTION OF SPECIFIC EMBODIMENTS

The compositions and methods of the invention provide a dietary supplement useful for maintaining a state of wellness, particularly in the human male. The dietary supplement of the invention comprises a combination of L-arginine, ginseng, and ginkgo biloba, which is useful for enhancing or improving blood flow and circulation. Improved blood flow is important for maintaining good cardiac and sexual health. The compositions and methods of the invention enhance sexual wellness without any undesirable side effects such as headache, nausea, gastric upset, chest pain, dizziness, vision disturbance, or change in blood pressure.

The main component of the composition of this invention is arginine. Arginine is an essential amino acid having the chemical name 2-amino-5-guanidinovaleric acid. It is used in the physiologically active form which is designated as the "L(+)" form. The compound is readily available from various sources in the commercial market place such as from Sigma Chemical Company or Aldrich Chemical Company in a pharmaceutical grade. It generally is available as a powder that generally is associated with two moles of water and forms monoclinic plates.

The second component present in the composition is ginseng. Ginseng is material extracted from the root of a plant that is a member of the ginseng family (*Araliaceae*), genus *Panax*. Ginseng plants grow in Asia and North America. *P. ginseng* grows in Northern China (Chinese ginseng) and Korea (Korean ginseng). The material extracted from the root is referred to as white ginseng or red ginseng. The former is dried *P. ginseng* root, while the latter is *P. ginseng* root steamed in caramel. American ginseng (*P. quinquefolium*) generally grows in the northern U.S. and Canada. Other relatives include Japanese ginseng (*P. japonicum*), San-Chi ginseng (*P. notoginseng*), Himalayan ginseng (*P. pseudoginseng*, ssp. *himalaicus* var *argustifolius*), and Siberian ginseng (*Eleutherococcus senticosus*).

The ginseng component in a tablet, capsule, or powder is usually standardized ginseng obtained from plants originating from one or more geographical areas, and comprises, in total, about 1% to about 50% ginsenosides, preferably about 10% to about 35% ginsenosides, more preferably about 15% to about 20% ginsenosides, most preferably about 17.5% ginsenosides. Preferably the ginseng component comprises American ginseng and Korean ginseng. The American ginseng comprises about 1%

to about 50% ginsenosides, preferably about 1% to about 10% ginsenosides, more preferably about 5% ginsenosides. The Korean ginseng comprises about 1% to about 50% ginsenosides, preferably about 10% to about 40% ginsenosides, more preferably about 30% ginsenosides. The ginseng component in a liquid or tonic is usually one or more extracts of ginseng from various geographical areas having a ratio of herb to solvent when extracted of about 1:2 to about 1:10, preferably about 1:5.

The various types of ginseng are available on the commercial market and are available from various sources, such as, for example, East Earth Herb and Natural Sourcing Solutions, Inc. The types and relative abundance of the chemical constituents of ginseng depend on the species, the part of the plant, the place of origin, the method of cultivation, and the technique of extraction used to obtain the ginseng. Different types of ginseng may have slightly different constituent profiles, but the type of ginseng used in this composition will be the material extracted from *Panax ginseng* or *Panax quinquefolius*. Preferably a mixture of American ginseng and Korean ginseng is employed.

The composition of the ginseng extracted from the roots of the various plants is quite similar among the different species used. Generally the ginseng will contain typical ginsenosides. A further discussion of the constituents of the various types of ginseng may be found in the American Chemical Society publication entitled "Folk Medicine: The Art and the Science," edited by Richard P. Steiner, University of Utah (1986).

The third essential ingredient in the composition of this invention is *Ginkgo biloba*, which is extracted from the leaves of the ginkgo biloba tree. The leaves are harvested in late summer when the leaves have the highest level of active compounds. The extract is semipurified to remove undesirable compounds which do not contribute to the desired health benefits. The material can be highly concentrated and standardized to a known and consistent level of the active principals known as ginkgolides. Ginkgo biloba is readily available from the various sources throughout the herbal medicine industry, such as, for example, East Earth Herb and Natural Sourcing Solutions, Inc..

The ginkgo component in a tablet, capsule, or powder is usually standardized ginkgo and comprises about 1% to about 50% flavone glycosides, preferably about 15% to about 30% flavone glycosides, more preferably about 24% flavone glycosides,

and about 1% to about 20% terpene lactones, preferably about 5% to about 10% terpene lactones, more preferably about 6% terpene lactones. The ginkgo component in a liquid or tonic is usually an extract having a ratio of herb to solvent when extracted of about 1:2 to about 1:5, preferably about 1:2.

The dietary supplement comprising the combination of L-arginine, ginseng, and ginkgo biloba is administered to a subject orally as a capsule or tablet or as an aqueous composition. If administered as a capsule, tablet, or powder, an amount of each of the three constituents is mixed in accordance with standard pharmaceutical practice to form a unit dosage that can be swallowed by taking water with the unit dosage. (See, for example, "Remington, The Science and Practice of Pharmacy," Nineteenth Edition, Mach Publishing co. for a discussion of the preparation of tablets and capsules/chapters 91-93). In general, the size of the tablet or capsule will be less than about a gram to maximize the ease of swallowing. In addition to the three major components of the dietary supplement of this invention, the composition also may contain antioxidant vitamins, vitamin-B-complex, and certain minerals. These additional constituents may be present in an amount up to about 100% of the daily values for each constituent. By "daily values" is meant the Reference Daily Intake (RDI) as defined in 21 CFR §101.9(c)(8)(iv). Antioxidant vitamins include vitamins A (preferably as palmitate), C (preferably as ascorbic acid) and E (preferably as dl α tocopherol acetate). Vitamin-B complex includes thiamin (preferably as the mononitrate), riboflavin, niacin (preferably is niacinamide), vitamin B-6 (preferably as pyroxidine HCl), folate (preferable as folic acid), vitamin B-12 (preferably as cyanocobalamin), biotin, and pantothenic acid (preferably as calcium pantothenate). Minerals include zinc (preferably as zinc gluconate), calcium (preferably as calcium carbonate, iron (as iron gluconate), and selenium (preferably as sodium selenate).

Where the dietary supplement of this invention is administered in tablet, capsule, or powder form, the daily dosage can be administered in single or multiple unit dosages, preferably 1 to 10 unit dosages, more preferably 4-6 unit dosages. The constituents are combined to form a unit dosage in accordance with the amounts set forth in Table I, in which the broad, preferred, and more preferred range is are set forth as milligrams (mg) or % Daily Values.

Table I

Constituent	Broad	Preferred	More Preferred
Arginine	250-750 mg	300-600 mg	450-550 mg
Ginseng	15-50 mg	20-40 mg	25-35 mg
Ginkgo biloba	5-15 mg	5-10 mg	5-10 mg
Antioxidant vitamins	0-100%	5-50%	10-20%
B-complex	0-100%	5-50%	10-20%
Minerals	0-100%	5-30%	10-20%

Where the dietary supplement of this invention is an aqueous composition, it may be administered as single or multiple drinks having a volume of up to 500 milliliters (ml) or more. Preferably however it is prepared as a drink having a volume of about 50 to about 250 ml with appropriate flavoring to be consumed either as a cold or hot beverage. Preferably it is flavored with a sweetener and a flavoring agents for easier consumption. A daily dose of two drinks each of about 100 ml has been found to be particularly useful. Table II sets forth the broad, preferred, and most preferred amounts in which the constituents are combined to form a unit dosage of 100 ml.

Table II

Constituent	Broad	Preferred	More Preferred
Arginine	500-10000 mg	750-3000 mg	1000-2000 mg
Ginseng	25-600 mg	100-400 mg	150-250 mg
GBE	12.5-300 mg	50-250 mg	50-150 mg
Antioxidant vitamins	0-200%	25-150%	50-100%
B-complex	0-200%	25-150%	50-100%
Minerals	0-100%	25-100%	50-100%

It should be appreciated that some vitamins and minerals, particularly some of the fat soluble vitamins, zinc, and selenium can be harmful in large doses. Thus, preferably the daily dosage of such vitamins and minerals should not exceed 200% Daily Values. If present, preferred daily dosages of the preferred minerals include about 15-30 mg zinc and about 70 mcg to about 140 mcg selenium. Preferred daily dosages of the preferred vitamin antioxidants include about 5000 IU to about 10000 IU Vitamin A, about 60 mg to about 120 mg Vitamin C, and about 30 IU to about 60 IU Vitamin E. Preferred daily dosages of the preferred B-vitamins include about 1.5 mg to about 3 mg thiamin, about 1.7 mg to about 3.4 mg riboflavin, about 2 mg to about 4 mg Vitamin B-6, and about 6 mcg to about 12 mcg Vitamin B-12. Preferred dosages of some other preferred vitamins include about 20 mg to about 40 mg niacin, about 400 mcg to about 800 mcg folate, about 300 mcg to about 600 mcg biotin, and about 10 mg to about 20 mg pantothenic acid.

The dietary supplement can be administered in tablet, capsule, liquid, powder or effervescent form. Methods of preparation of formulations for various forms of administration are known in the art and discussed in detail in Remington's Pharmaceutical Sciences, Eighteenth Edition (1990), incorporated herein by reference. Tablets, for example, can include components in addition to the active ingredients, such as diluents, binders, lubricants, glidants, disintegrants, coloring agents, and flavoring agents. Capsules, for example, are made largely from gelatin,

FD&C colorants, and sometimes an opacifying agent such as titanium dioxide. Effervescent tablets, for example, comprise in addition to the active ingredients, sodium bicarbonate and an organic acid such as tartaric acid or citric acid. In the presence of water, these additives react, liberating carbon dioxide as a result of an acid-base reaction, which acts as a disintegrator and produces effervescence. Concentrations of the additives vary according to the acidic or basic nature of the active ingredients in order to ensure that an acid-base reaction occur upon contact of the effervescent tablet with water. The dietary supplement can also be formulated as a powder, which can be ingested directly or which can be ingested after reconstitution with an aqueous liquid. Preferably the supplement is administered in a capsule, effervescent tablet, or as a liquid tonic. The formulations can also comprise a flavoring agent.

Method of Administration

Another aspect of this invention is a method for enhancing blood circulation in a human subject. The method comprises administering as unit dosage a dietary supplement comprising the combination of L-Arginine, ginseng, ginkgo biloba. By enhancing the blood circulation in a human subject, the overall wellness of a person is enhanced and, specifically, better blood circulation results in a healthier sex life, improved mental performance, and improved cardiovascular health. In particular, when the composition is administered to a human male, it is found that the male is able to improve the ability to achieve an erection. In addition it is found that the erection can be maintained for a period of time that is longer than would occur without the administration of the dietary supplement. In addition, it has been found that the quality of the orgasm for the subject receiving the dietary supplement is improved noticeably. Thus the sexual fitness of the subject is experienced or improved for an individual. In addition, it is found that upon exertion by any significant exercise the subject's breathing and ability to breathe is improved.

The dietary supplement increases the production of nitric oxide (NO) by providing more substrate (L-arginine) for its production and upregulating the activity of nitric oxide synthase (NOS), the enzyme that cleaves L-arginine to form NO. NO in turn signals the creation of cGMP which triggers an erection in men. The dietary supplement helps improve the body's production of cGMP. Female sexual function is

accomplished physiologically in a similar manner. For example, cGMP triggers lubrication and engorgement of the clitoral tissue. Thus, the dietary supplement of the invention is useful for enhancing overall wellness, particularly sexual wellness, in both men and women. The dietary supplement can also be used in a method of medical treatment, such as, for example, the treatment of sexual dysfunction, or for the preparation of a medicament for such treatment.

As shown in Example 7, simultaneous usage of Viagra™ (sildenafil citrate) and a dietary supplement comprising L-arginine, ginseng and ginkgo biloba improves sexual function in patients who did not respond satisfactorily to Viagra™ alone. Viagra™, which is currently prescribed in 25, 50 and 100 mg dosages for erectile dysfunction, exerts its effects by transiently inhibiting PDE5, a chemical in the body responsible for the degradation of cGMP in the corpus cavernosum (penis cavity). In essence, Viagra™ decreases the body's ability to breakdown cGMP for a short time, allowing more of it to accumulate. The resulting higher levels of cGMP increases the ease in achieving and maintaining an erection.

Alpostradil is a smooth muscle relaxant. The binding of alprostadil to its receptors is accompanied by an increase in intracellular cAMP levels. Human cavernous smooth muscle cells respond to alprostadil by releasing intracellular calcium into the surrounding medium. Smooth muscle relaxation is associated with a reduction of the cytoplasmic free calcium concentration. Alprostadil also attenuates pre-synaptic noradrenaline release in the corpus cavernosum, which is essential for the maintenance of a flaccid and non-erect penis.

The dietary supplement, Viagra ™, and alprostadil all work to facilitate smooth muscle relaxation and vascular dilatation. Thus, yet another aspect of this invention is a method for enhancing the response of a male subject to a pharmaceutical composition which facilitates smooth muscle relaxation and vascular dilatation, preferably which increases the levels of cGMP in the corpus cavernosum. The method is useful for subjects which have an unsatisfactory response to the pharmaceutical composition and wish to improve the efficacy of the pharmaceutical composition. The method comprises administering a daily dosage of a dietary supplement comprising, in at least one unit dosage, L-arginine, ginseng, and ginkgo biloba for a number of days sufficient to improve the ability of the subject to achieve penile erection when the pharmaceutical composition is administered. Preferably the

dietary supplement is administered for at least one day, more preferably at least about one week, and most preferably at least about two weeks. Other compounds which increase the levels of cGMP include, but are not limited to, alprostadil.

The invention also provides a method for reducing the pharmaceutically effective dose of a pharmaceutical composition, such as, *e.g.*, a composition comprising sildenafil citrate and/or alprostadil, which facilitates smooth muscle relaxation and vascular dilatation, preferably which increases the levels of cGMP in the corpus cavernosum. The method is useful for subjects who, having experienced undesirable side effects with their current dosage of the pharmaceutical composition, wish to reduce the dosage to avoid the side effects yet maintain a favorable level of efficacy. The method is also useful for subjects who do not have problems with side effects from the current dosage of the pharmaceutical composition but wish to achieve the same level of efficacy with a reduced dosage for reasons of cost, preference for natural products, etc. The method comprises administering, to a male subject being treated with a first dosage of the pharmaceutical composition, a daily dosage of a dietary supplement comprising, in at least one unit dosage, L-arginine, ginseng, and ginkgo biloba for a time sufficient to enhance the effects on said cGMP levels mediated by a first dosage of a pharmaceutical composition prescribed for erectile dysfunction; and adjusting said first dosage to a second dosage which exerts the same effects on said cGMP levels of said first dosage prior to commencement of said daily dosage of said dietary supplement.

Another preferred aspect of the invention is a method of ameliorating erectile dysfunction, comprising administering a daily dosage of a dietary supplement comprising L-arginine, ginseng, and ginkgo biloba and administering, when an erection is desired, a pharmaceutical composition, such as, *e.g.*, a composition comprising sildenafil citrate and/or alprostadil, which facilitates smooth muscle relaxation and vascular dilatation, preferably which increases the levels of cGMP in the corpus cavernosum. Typically, the pharmaceutical composition is administered less than about 6 hours before attempting intercourse, preferably from about 4 hours to about 0.5 hour before sexual activity, and most preferably about 1 hour before sexual activity. Preferred dosages of the pharmaceutical composition are about one fourth of the dosages normally prescribed, preferably about one half of the normal

dosages. For example, preferred dosages of sildenafil citrate for this method include, but are not limited to, about 6.25 mg, 12.5 mg, 25 mg, and 50 mg dosages.

In general, the administration of the composition of this invention is carried out on a daily basis for at least two days. Preferably it is administered for at least about a one week period, more preferably at least about a two week period, most preferably for at least about a four week period, and is most preferably carried out over an extended period of time making the dietary supplement an addition to the diet on a sustained basis. In administering the composition to an individual, the composition is administered in either the tablet capsule or liquid form in accordance with the composition discussed herein before. Typically, a desired daily dosage is achieved by administering an appropriate quantity of unit dosages. Generally the amounts administered on a daily basis will be between about 500 mg - 10000 mg of L-arginine per day, preferably about 2000 to 5000 mg of L-arginine a day. The ginseng is administered at a rate of about 25 mg to about 600 mg per day preferably about 100 to about 400 mg per day. The ginkgo biloba is administered at a rate of about 8 mg to 300 mg per day, preferably about 50 to about 250 mg per day. Optionally up to 200 percent of the daily values of antioxidant vitamins, vitamin B complex and certain minerals, as discussed hereinbefore, are administered along with the dietary supplement combination.

The supplement can be administered weekly or even monthly, but daily administration is preferred, preferably on an empty stomach. The daily dosage can be a single unit dosage or a multiple unit dosage. For example, a daily dosage can be from 1 to 10 capsules or 1 to 4 100 ml beverages daily. Preferably the daily dosage is 6 capsules or 2 100 ml beverages. Preferably the daily dosage is administered in two unit dosages, preferably upon waking and at bedtime. Some preferred dietary supplements are discussed further in Examples 1-3.

EXAMPLES

Example 1 - Dietary Supplement in Gel Cap Form

The dietary supplement is provided in a 6 gel cap serving to be taken daily, preferably by a human male, for at least 2-3 weeks, preferably on an empty stomach, and comprises the following components per serving:

Vitamin A	5000IU
Vitamin C	60 mg
Vitamin E	30 IU
Thiamin	1.5 mg
Riboflavin	1.7 mg
Niacin	20 mg
Vitamin B-6	2 mg
Folate	400 mcg
Vitamin B-12	6 mcg
Biotin	300 mcg
Pantothenic acid	10 mg
Zinc	15 mg
Selenium	70 mcg
L-arginine	3000 mg
American Ginseng - standardized (5% ginsenosides)	100 mg
Korean Ginseng - standardized (30% ginsenosides)	100 mg
Ginkgo Biloba - standardized (24% flavone glycosides, 6% terpene lactones)	50 mg

Other ingredients: Rice Flour Powder, Magnesium Stearate, Silica

Example 2 - Dietary Supplement in Tonic Form

The dietary supplement is provided in two 100 ml servings to be taken daily, preferably by a human male, for at least 2-3 weeks, preferably on an empty stomach, and comprises the following components per serving:

Vitamin A	5000 IU	
Vitamin C	60 mg	
Vitamin E	30 IU	
Thiamin	1.5 mg	
Riboflavin	1.7 mg	
Niacin	20 mg	
Vitamin B-6	2 mg	
Folate	400 mcg	
Vitamin B-12	6 mcg	
Biotin	300 mcg	
Pantothenic acid	10 mg	
Zinc	7.5 mg	
Selenium	70 mcg	
L-arginine	1500 mg	
American Ginseng - root (1:5)		100 mg
Korean Ginseng - root (1:5)		100 mg
Ginkgo Biloba - fresh leaf (1:2)		100 mg

Other ingredients: Filtered Water, High Fructose Corn Syrup, Strawberry Concentrate, Citric Acid, Natural Flavors

Example 3 - Dietary Supplement in Gel Cap Form

The dietary supplement is provided in a 6 gel cap serving to be taken daily, preferably by a human female, for at least 2-3 weeks, preferably on an empty stomach, and comprises the following components per serving:

Vitamin A	5000IU
Vitamin C	60 mg
Vitamin E	30 IU
Thiamin	1.5 mg
Riboflavin	1.7 mg
Niacin	20 mg
Vitamin B-6	2 mg
Folate	400 mcg
Vitamin B-12	6 mcg
Biotin	300 mcg
Pantothenic acid	10 mg
Calcium	500 mg
Iron	9 mg
Zinc	75 mg
L-arginine	2500 mg
Korean Ginseng - standardized (30% ginsenosides)	100 mg
Ginkgo Biloba - standardized (24% flavone glycosides, 6% terpene lactones)	50 mg
Daminana leaves (Turnera Aphrodisiaca)	50 mg

Other ingredients: Rice Flour Powder, Magnesium Stearate, Silica

Example 4 - Regular administration of L-arginine to maintain a state of wellness thereby reducing the likelihood of developing a headache

A healthy man takes 3000 mg L-arginine as a separate dietary supplement daily on an empty stomach for a minimum of 2-3 weeks.

Example 5 - Regular administration of L-arginine in combination with ginseng and ginkgo biloba to maintain a state of wellness

18 healthy men, age 29 to 44, were instructed to take two 100 ml servings of the dietary supplement described in Example 2 daily on an empty stomach for eight weeks. Survey data was collected before and after the men begin taking the dietary supplement. The volunteers noted a 29 to 33% increase in quality of orgasm, sexual confidence and sexual stamina. Penile hardness ratings and sexual enjoyment ratings increased by 13%. Ease of breathing after exertion also increased by 29%. Frequency of headaches decreased.

Example 6 – Administration of L-arginine in combination with ginseng and ginkgo biloba in men with erectile dysfunction

Male subjects with mild to moderate erectile dysfunction were instructed on the use and regimen of the dietary supplement of Example 1 and were requested to fill our a baseline SFQ survey. Subjects started a twice-per-day regimen of the dietary supplement, once in the morning upon waking and once in the evening at bedtime. A 4-week supply of the dietary supplement was provided. After completing the 4-week regimen, patients were instructed to complete a 4-week SFQ survey and return to the test center for follow-up evaluation and examination.

The SFQ was used as the primary test instrument. The SFQ is a self-administered questionnaire beginning with the validated IIEF (International Index of Erectile Function used with permission) test instrument and including other validated test instruments designed to measure changes in erectile function, sexual function, and quality of life. (Rosen et al., Urology, June 1997, 49(6):822-830; Derogatis LR, J Sex Marital Ther, 1997, 23(4):291-304; Conte HR, Arch Sex Behav, December 1983, 12(6):555-576; Jenkinson et al., BMJ, May 29, 1993, 306(6890):1437-1440; Garrarr et al., BMJ, May 29, 1993, 306(6890):1440-1444) In addition, the SFQ included questions regarding subject's activities and condition during the trial period.

Subject Group Profile At Baseline:

Total # of subjects	25
Age range	40-77
# hypertensive	19
# diabetes mellitus	4

Patient responses to SFQ survey questions at 4 weeks were compared to SFQ responses at baseline. A comparison analysis was performed for those subjects whose degree of erectile dysfunction were mild to moderate as characterized by a minimal baseline score of 2. For each SFQ variable, a comparison was made of those subjects who initially had a baseline score of at least 2 to their 4 week score on the same variable. The results were then pooled, summarized, and evaluated to reflect the percentage of subjects with improvement in each of the SFQ question variables. 88.9% of subjects showed improvement in the ability to maintain erection during intercourse. 75.0% of subjects showed improvement in satisfaction with overall sex life. 20.0% of subjects showed improvement in number of orgasms. 12.5% of subjects showed improvement in the number of times attempted intercourse.

There were no significant changes in blood pressure or other significant side effects as noted by net % of patients reporting increase or decrease as follows:

Headaches:	-4.8%
Nausea:	-4.8%
Stomach upset:	-14.3%
Chest pain:	0%
Dizziness:	0%
Vision disturbance:	0%

Example 7 - Administration of L-arginine in combination with ginseng and ginkgo biloba in patients that had not responded satisfactorily to Viagra™

Six patients which had not responded satisfactorily to Viagra™ (sildenafil citrate) were asked to use the dietary supplement of Example 1 for 4 weeks on a daily basis and to try Viagra™ again as they felt the need. Typically patients used Viagra™ about 1 hour prior to engaging in sexual activity. Patients were using either

50 or 100 mg dosages of Viagra™ . 4 out of 6 showed dramatic improvement based on an increase in several key IIEF variables, such as erection frequency, erection firmness, penetration ability, maintenance frequency, and maintenance ability.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A dietary supplement for wellness, comprising in a unit dosage a combination of (a) L-arginine, (b) ginseng, and (c) ginkgo biloba.

2. The dietary supplement of Claim 1, wherein said unit dosage is a capsule or a tablet.

3. The dietary supplement of Claim 2 comprising

(a) about 250 mg to about 750 mg L-arginine,

(b) about 15 mg to about 50 mg ginseng, and

(c) about 5 mg to about 15 mg ginkgo biloba

4. The dietary supplement of Claim 3, that further comprises in a unit dosage an amount of antioxidant vitamins, vitamin B complex, and minerals sufficient to provide up to 100% of the percent daily values of the antioxidant vitamins, vitamin B complex, and minerals upon administering an appropriate quantity of the unit dosages to achieve a desired daily dosage.

5. The dietary supplement of Claim 4, comprising

(a) about 300 mg to about 600 mg L-arginine,

(b) about 20 mg to about 40 mg ginseng, and

(c) about 5 mg to about 10 mg ginkgo biloba

6. The dietary supplement of Claim 1, wherein the unit dosage is an aqueous composition.

7. The dietary supplement of Claim 6, comprising

(a) about 500 mg to about 5000 mg L-arginine,

(b) about 25 mg to about 600 mg ginseng, and

(c) about 12.5 mg to about 300 mg ginkgo biloba

8. The dietary supplement of Claim 7, that further comprises in a unit dosage an amount of antioxidant vitamins, vitamin B complex, and minerals sufficient to provide up to 100% of the percent daily values of the antioxidant vitamins, vitamin B complex, and minerals upon administering an appropriate quantity of the unit dosages to achieve a desired daily dosage.

9. The dietary supplement of Claim 8, having daily dosage amount of about 50 ml to about 250 ml.

10. The dietary supplement of Claim 8, comprising

(a) about 750 mg to about 3000 mg L-arginine,

(b) about 100 mg to about 400 mg ginseng, and

(c) about 50 mg to about 250 mg ginkgo biloba

11. The dietary supplement of Claim 10, which is an aqueous drink of about 100 ml comprising

(a) about 1500 mg L-arginine;

(b) about 100 mg American ginseng and about 100 mg Korean ginseng;

(c) about 100 mg ginkgo biloba;

(d) about 100% of the daily value of each of vitamins A, C, and E;

(e) about 100% of the daily value of each of thiamin, riboflavin, niacin, vitamin B-6, folate, vitamin B-12, biotin, pantothenic acid; and

(f) about 50% of the daily value of zinc and about 100% of the daily value of selenium.

12. The dietary supplement of Claim 1, wherein said supplement is for men's wellness.

13. The dietary supplement of Claim 1, wherein said supplement is For women's wellness.

14. A method for enhancing blood circulation in a human subject, which method comprises administering a sufficient quantity of unit dosages of a dietary supplement to achieve a desired daily dosage, the unit dosage comprising

(a) L-arginine,

(b) Ginseng, and

(c) Ginkgo biloba

15. The method of Claim 14 wherein the dietary supplement is unit dosage in the form of a capsule or a tablet.

16. The method of Claim 15, wherein the unit dosage comprises

(a) about 250 mg to about 750 mg L-arginine,

(b) about 15 mg to about 50 mg ginseng, and

(c) about 5 mg to about 10 mg ginkgo biloba

17. The method of Claim 16, wherein the desired daily dosage of the dietary supplement comprises up to 100% of the percent daily values of antioxidant vitamins, vitamin B complex, and minerals.

18. The method of Claim 17, wherein the unit dosage comprises

(a) about 300 mg to about 600 mg L-arginine,

(b) about 20 mg to about 40 mg ginseng, and

(c) about 5 mg to about 10 mg ginkgo biloba

19. The method of Claim 14, wherein the dietary supplement is an aqueous composition.

20. The method of Claim 19, wherein the unit dosage comprises

(a) about 500 mg to about 5000 mg L-arginine,

(b) about 25 mg to about 600 mg ginseng, and

(c) about 12.5 mg to about 300 mg ginkgo biloba

21. The method of Claim 20, wherein the desired daily dosage of the dietary supplement comprises up to 200% of the percent daily values of antioxidant vitamins and vitamin B complex, and up to 100% of the percent daily value of minerals.

22. The method of Claim 21, wherein the unit dosage is delivered as a beverage of about 50 ml to 250 ml.

23. The method of Claim 22, wherein the dietary supplement comprises

(a) about 750 mg to about 3000 mg L-arginine,

(b) about 100 mg to about 400 mg ginseng, and

(c) about 50 mg to about 250 mg ginkgo biloba

24. The method of Claim 22, wherein the aqueous composition is a drink of about 100 ml comprising

(a) about 1500 mg L-arginine;

(b) about 100 mg American ginseng and about 100 mg Korean ginseng;

(c) about 100 mg ginkgo biloba;

(d) about 100% of the daily value of each of vitamins A, C, and E;

(e) about 100% of the daily value of each of thiamin, riboflavin, niacin, vitamin B-6, folate, vitamin B-12, biotin, pantothenic acid; and

(f) about 50% of the daily value of zinc and about 100% of the daily value of selenium.

25. The method of Claim 14, wherein the combination is administered to the subject daily for at least two weeks.

26. The method of Claim 14, wherein the combination is administered daily to a male subject for a time sufficient to improve the ability of the subject to achieve penile erection.

27. The method of Claim 14, wherein the combination is administered daily to a male for a time sufficient for the male to maintain an erection for a period of time longer than without the administration of the combination.

28. The method of Claim 14, wherein the combination is administered to a subject for a time sufficient to improve the quality of orgasm for the subject.

29. The method of Claim 15, wherein the dietary supplement is administered to the subject for a period of time sufficient to improve the sexual fitness of the subject.

30. The method of Claim 15, wherein the dietary supplement is administered for a period of time sufficient for the subject to experience easier breathing upon exertion.

31. A method for enhancing the response of a male subject to a pharmaceutical composition which facilitates smooth muscle relaxation and vascular dilatation, comprising administering a daily dosage of a dietary supplement comprising, in at least one unit dosage, L-arginine, ginseng, and ginkgo biloba for a number of days sufficient to improve the ability of the subject to achieve penile erection when said pharmaceutical composition is administered.

32. The method of Claim 31, wherein said pharmaceutical composition increases the levels of cGMP in the corpus cavernosum.

33. The method of Claim 32, wherein said pharmaceutical composition comprises a compound which inhibits the degradation of cGMP in said corpus cavernosum.

34. The method of Claim 31, wherein said pharmaceutical composition comprises sildenafil citrate.

35. The method of Claim 31, wherein said pharmaceutical composition comprises alprostadil.

36. The method of Claim 31, wherein said daily dosage is administered for at least two weeks.

37. A method for reducing the pharmaceutically effective dose of a pharmaceutical composition which increases the levels of cGMP in the corpus cavernosum, comprising

administering, to a male subject being treated with a first dosage of said pharmaceutical composition, a daily dosage of a dietary supplement comprising, in at least one unit dosage, L-arginine, ginseng, and ginkgo biloba for a time sufficient to enhance the effects on said cGMP levels mediated by said first dosage of said pharmaceutical composition; and

adjusting said first dosage to a second dosage which exerts the same effects on said cGMP levels of said first dosage prior to commencement of said daily dosage of said dietary supplement.

38. The method of Claim 37, wherein said male subject is being treated for erectile dysfunction.

39. A method of ameliorating erectile dysfunction, comprising administering a daily dosage of a dietary supplement comprising L-arginine, ginseng, and ginkgo biloba and administering, before attempting sexual intercourse, a pharmaceutical composition which facilitates smooth muscle relaxation and vascular dilatation.

40. The method of Claim 39, wherein said pharmaceutical composition increases the levels of cGMP in the corpus cavernosum.

41. The method of Claim 40, wherein said pharmaceutical composition comprises a compound which inhibits the degradation of cGMP in said corpus cavernosum.

42. The method of Claim 39, wherein said pharmaceutical composition comprises sildenafil citrate.

43. The method of Claim 39, wherein said pharmaceutical composition comprises alprostadil.

44. A method of improving sexual function in a subject, comprising administering a sufficient quantity of unit dosages of a dietary supplement to achieve a desired daily dosage, the unit dosage comprising

(a) about 250 mg to about 750 mg L-arginine,

(b) about 15 mg to about 50 mg ginseng, and

(c) about 5 mg to about 10 mg ginkgo biloba.

45. The method of Claim 44, wherein the subject is a human male.

46. The method of Claim 44, wherein the subject is a human female.

47. A method of treating sexual dysfunction in a subject, comprising administering a sufficient quantity of unit dosages of a dietary supplement to achieve a desired daily dosage, the unit dosage comprising

(a) about 250 mg to about 750 mg L-arginine,

(b) about 15 mg to about 50 mg ginseng, and

(c) about 5 mg to about 10 mg ginkgo biloba.

48. A composition comprising, in at least one unit dosage, L-arginine, ginseng, and ginkgo biloba for use in a method of medical treatment.

49. Use of a composition comprising, in at least one unit dosage, L-arginine, ginseng, and ginkgo biloba for the preparation of a medicament for the treatment of sexual dysfunction.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07427

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K35/78 A61K31/195 A61K31/505 //(A61K35/78,31:195, 31:505)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE PROMT 'Online! The Gale Group Dialog File 16, Accession number 05089300, 1994 PRODUCT ALERT MAY 9, 1994: "Golf Pro Nutrition Bar" XP002110279 * see the abstract * abstract ---	1,12,13
Y	DATABASE WPI Section Ch, Week 9732 Derwent Publications Ltd., London, GB; Class B04, AN 97-342453 XP002110280 & CN 1 107 349 A (WANXIAN CITY PHARM PLANT), 30 August 1995 (1995-08-30) abstract --- -/--	1-49

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 1999	11.08.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Isert, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 99/07427

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	NIERI, ALDO DOMINGCO: "Comparative evaluation of a therapeutic association in the treatment of stress." PRENSA MEDICA ARGENTINA, (1992) VOL. 79, NO. 5, PP. 272-276. , XP002110277 *see in particular p. 276 "summary", and p. 274 "Tabla 3"*	1-49
Y	CHEN X ET AL: "Ginsenosides -induced nitric oxide-mediated relaxation of the rabbit corpus cavernosum." BRITISH JOURNAL OF PHARMACOLOGY, (1995 MAY) 115 (1) 15-8. , XP002110278 * see in particular the abstract *	1-49
Y	WO 94 01006 A (BIO NUTRITIONAL HEALTH SERVICE :STEPHAN PETER MALCOLM (GB)) 20 January 1994 (1994-01-20) *see in particular examples 1,15,19 *	1-49
Y	US 5 730 987 A (OMAR LOTFY ISMAIL) 24 March 1998 (1998-03-24) *see in particular claims 1,6,8; col. 7, line 30 - col. 8. line 6*	1-49

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/07427

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ICID: <WO___9951252A1_I_>

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99/07427

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 14-47 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Present claims 31-33,37-41 relate to a method wherein a composition is defined by reference to a desirable characteristic or property, namely "composition which facilitates smooth muscle relaxation and vascular dilatation", "composition which increases the levels of cGMP ..", etc. The claims cover all compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compositions as defined in dependent claims 34,35,42,43, and the method as defined in dependent claim 38, having regard to the example 7.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/US 99/07427

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 1107349 A	30-08-1995	NONE	
WO 9401006 A	20-01-1994	AU 4509993 A	31-01-1994
		GB 2268871 A	26-01-1994
US 5730987 A	24-03-1998	NONE	